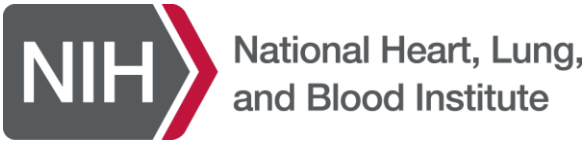

New FOAs for Investigator-Initiated Phase II and Above Multi-site Clinical Trials

Frequently Asked Questions

June 22, 2016

The New FOAs for Multi-site Clinical Trials

Q. What is a "clinical trial" for the purpose of these FOAs?

A. The Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) FOAs apply to clinical trials as defined by NIH (see below) that enroll participants at two or more recruitment sites. The FOAs are not intended to support single-site clinical trials, first-in-human/Phase I trials, or multi-site observational studies that do not fit the NIH definition of a clinical trial (NOT-OD-15-015).

The NIH definition of *clinical trial* is (NOT-OD-15-015):

> A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Q. How is "Phase II" defined for the purpose of applying for multi-site clinical trial funding under these FOAs?

A. Phase II clinical trials are those being conducted to obtain preliminary data on the efficacy of a drug, device, biologic, or other clinical intervention. This phase of testing also helps determine the common short-term side effects and risks associated with the intervention. Phase II studies are typically well-controlled, closely monitored, trials and may enroll up to several hundred participants with the target condition. In contrast, a trial introducing an agent into a human for the first time, or for a new indication, that is aimed primarily at understanding the safety profile of an agent would be considered a Phase I (rather than a Phase II) and would not be responsive to these new multi-site clinical trial FOAs.

Q. Why are changes being made at this time to the way NHLBI solicits multi-site clinical trials?

A. The new FOAs are intended to enhance the selection, conduct, and oversight of NHLBI multi-site clinical trials through the identification, inclusion, and application of well-defined performance milestones. This approach will enhance selection of trials that are operationally feasible and promote the ability of multi-site clinical trials in

Phase II and above to complete on budget, on time, and according to the originally-planned objectives of the study. Performance milestones will be identified by the investigators and reviewed by NHLBI, thus establishing shared expectations regarding trial performance. NHLBI will use the performance milestones to monitor and oversee trial conduct and results dissemination.

Q: What specific changes are in the new NHLBI's FOAs for multi-site clinical trials?

A. Some of the more notable changes include:

- Requesting that a protocol synopsis be included as an attachment, which will be part of the application that reviewers will be required to assess.
- Having applicants provide more detailed information up front on:
  - timelines and processes for reaching key milestones, including accrual targets,
  - data to support accrual projection, and
  - the proposed team's expertise in clinical trial conduct.
- Articulating in the FOA peer-review criteria that will ensure rigorous evaluation of both scientific impact and operational feasibility.
- Having both the CCC and the DCC applicants submit project management plans that outline strategies to proactively manage clinical trials, including continuing evaluation of potential barriers to scientific and clinical activities, upfront development of contingency plans, and timely implementation of solutions, as needed.
- For trials using an FDA regulated product, requiring that the results of the pre-IND/IDE meeting and FDA communications be provided in the application, and asking applicants to submit the IND/IDE to FDA at least a month before a potential award so that documentation of the FDA determination will be available to NHLBI prior to a possible award.
- Awards that include milestone-driven and performance-based expectations.
- Clinical coordinating center (CCC) and data coordinating center (DCC) awards made under distinct mechanisms, but that are coordinated and synchronized.
- Providing project support for five years with the potential for up to seven years if strongly justified.

For additional changes and more detail, please read the Funding Opportunity Announcements, available at

- Clinical Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials (Collaborative UG3/UH3)

- Data Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials (Collaborative U24)

Q: May I include in my application to the UG3/UH3 FOA a proposal for a pilot study to be conducted during the UG3 phase?

A: The UG3/UH3 mechanism is not intended to support pilot studies to establish the feasibility of the clinical trial. Pilot studies are funded by the R34 mechanism. However, the UG3 phase may be used to refine study procedures, such as imaging, clinical assessments, and laboratory tests, in support of a well-justified study design that is already based on appropriate pilot data.

Application submission and review process

Q: Will the review criteria change from those used previously?

A. Yes. The new FOAs articulate peer-review criteria that will promote rigorous evaluation of not only the study's scientific impact but also its operational feasibility. For example, the reviewers will be asked to review the milestone plan and the information provided to support accrual goals.

Q. Will this change the preapproval process for projects with a proposed direct cost budget of $500,000 or more?

A. No. If the combined direct costs of the DCC and CCC applications equal or exceed $500,000 in any one year, the investigator still must contact program staff to obtain documented approval in the form of a letter from the Institute stating that it will accept the application for initial peer review (at http://www.nhlbi.nih.gov/funding/policies/500kweb.htm). Program staff will continue to have consultations (staff visits) with the investigators (at least 8 weeks ahead of the desired receipt date) and involve any other relevant NHLBI staff. Investigators should submit a letter of request to the relevant Division Director, and if the project is approved, append the corresponding letter of approval to the cover letter of the CCC and DCC applications. The letter of approval needs to be submitted with the applications.

Even if the combined direct cost budget being proposed does not meet the $500,000 direct cost threshold, NHLBI nonetheless strongly encourages investigators to discuss their applications with NHLBI program staff.

Q. Will this change the NHLBI process for CCC and DCC applications with a proposed combined budget with direct costs of $1,515,000 or more in any one year?

A. No it will not. Applications that involve CCC and DCC requested budgets that together exceed $1.515 million (combined) in direct costs in any given year need to go to the Large Application Panel (LAP), undergo the preapproval process for applications with budgets of $500,000 or more in direct costs in any one year, and may still only be submitted twice a year. The letter of request must be submitted following the staff visit no later than November 15 or May 15, as applicable.

Q. I'm putting together an application for a Phase II (or above) multi-site clinical trial that I plan on submitting after the June/July 2016 submission dates. Should I follow the old FOA (PAR-13-128) or the new ones?

A. The last non-AIDS application dates under the old FOA are in June (new) and July 2016 (resubmission/renewal), so if you are submitting after those dates, you should prepare CCC and DCC applications that are compliant with the new cooperative agreement FOAs.

Q. I am an investigator at an institution outside the United States. Am I eligible to apply for the CCC and DCC awards under these FOAs?

A. Institutions outside the United States are eligible to apply for the CCC award. However, foreign institutions are not eligible to apply for the DCC award under the rules that apply to that award. It is acceptable, on the other hand, for a non-US component of a US institution to apply for a DCC award.

Q. I am planning to submit a new application under the old FOA with a June submission deadline. If I need to resubmit, may I submit an amended application under the old FOA or what should I do?

A. You would not be able to submit an amended application under the old FOA. You should first wait to get your overall impact score and discuss the summary statement with your Program Officer. If you decide you want to revise your applications and resubmit, you would need to submit your applications as new applications under the new FOAs, not as amended applications.

Q: If I revise my application with a budget at or above $500,000 in any one year and submit it as a new application under the new FOA, do I need to submit another letter of approval from NHLBI?

A. Yes, you do. In addition, we strongly encourage you to contact your NHLBI Program Officer to discuss the need for another consultation visit or call.

Currently funded trials

Q. I am running a trial that is already funded. Will I be expected to submit new information or adhere to new oversight requirements?

A. If you submit for renewal then the new FOAs' requirements apply; otherwise, an ongoing trial is subject to the terms of the Notice of Grant Award.

Q. I'm interested in applying for a clinical trial that I would like to conduct in collaboration with or through a Network. How can I apply? Must I apply under both FOAs (the one for the CCC and the DCC) even though the Network already has a DCC in place? If so, will the DCC application be evaluated against all the criteria specified for investigator-initiated multi-site clinical trials (Phase II and above) through a milestone-driven cooperative agreement (U24) award?

A. You will have to apply under the new FOAs with both a CCC and a DCC application. The latter will be coming from the Network DCC. The DCC application for a U24 award will be evaluated against the applicable criteria.

Investigator input

Q. Has the investigator community had input into these proposed changes?

A. Yes. In November 2015, NHLBI published a "Request for Information" on *Optimizing the NHLBI Clinical Trials Enterprise: Performance Milestones and Metrics*. NHLBI received robust input from many diverse stakeholders through this process. NHLBI has also consulted its advisory council, which is composed of scientists and clinicians in academic, industry, and clinical care settings. Collectively, that input informed the development of the new FOAs.